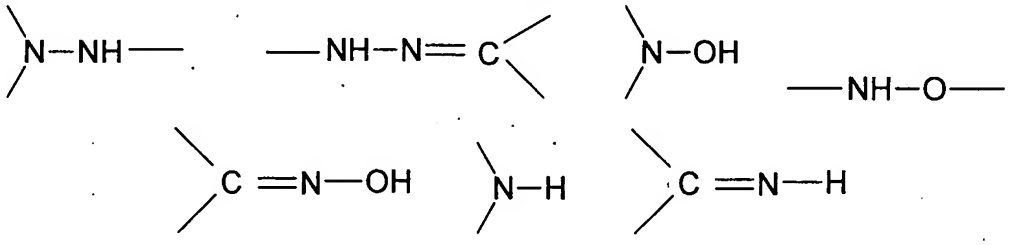
CLAIMS

1 - A method of creating a carbon-heteroatom bond by reacting a leaving group-bearing unsaturated compound and a nucleophilic compound introducing a heteroatom which can substitute for the leaving group, thereby creating a carbon-heteroatom bond, in the presence of a palladium-based catalyst, optionally a ligand, characterized in that the reaction takes place in the presence of an effective amount of a metal hydroxide or ammonium hydroxide, associated with an alcohol-type solvent.

2 - The method as claimed in claim 1, characterized in that the nucleophilic substrate is an organic hydrocarbon compound that may be both acyclic and cyclic and the characteristic of which is that it comprises at least one oxygen atom and/or at least one nitrogen atom bearing a free doublet: it being possible for said nitrogen atom to be introduced by means of a functional group, or included in a ring in the form of NH.

3 - The method as claimed in either of claims 1 and 2, characterized in that the nucleophilic substrate comprises at least one atom or group below:

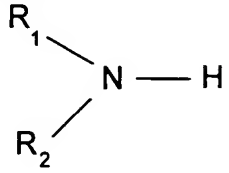


4 - The method as claimed in one of claims 1 to 3, characterized in that the nucleophilic substrate comprises at least one nitrogen atom bearing a free doublet included in a saturated, unsaturated or aromatic ring: the ring generally comprising from 3 to 8 atoms.

5 - The method as claimed in one of claims 1 to 4, characterized in that the nucleophilic substrate is a primary or secondary amine; an imine; an oxime; a hydroxylamine; a hydrazine; a hydrazone; a nitrogenous heterocycle.

6 - The method as claimed in claim 1, characterized in that the nucleophilic

substrate corresponds to the formula below:

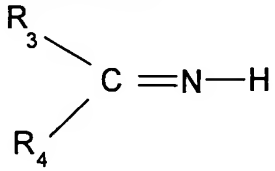


(Ia)

in said formula (Ia):

- R_1 and R_2 represent, independently of one another, a hydrogen atom or a hydrocarbon group having from 1 to 20 carbon atoms, which may be a linear or branched, saturated or unsaturated, acyclic aliphatic group; a monocyclic or polycyclic, saturated, unsaturated or aromatic carbocyclic or heterocyclic group; a chain of the abovementioned groups,
- at most one of the groups R_1 and R_2 represents a hydrogen atom.

7 - The method as claimed in claim 1, characterized in that the nucleophilic substrate corresponds to the formula below:

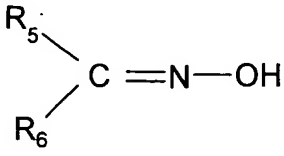


(Ib)

in said formula:

- R_3 and R_4, which may be identical or different, have the meaning given for R_1 and R_2 in formula (Ia),
- at most one of the groups R_3 and R_4 represents a hydrogen atom.

8 - The method as claimed in claim 1, characterized in that the nucleophilic substrate corresponds to the formula below:



(Ic)

in said formula:

- R_5 and R_6, which may be identical or different, have the meaning given for R_1 and R_2 in formula (Ia),
- at most one of the groups R_5 and R_6 represents a hydrogen atom.

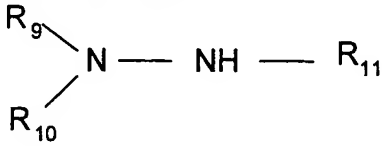
9 - The method as claimed in claim 1, characterized in that the nucleophilic substrate corresponds to the formula below:

(Id)

in said formula:

- R_7 has the meaning given for R_1 and R_2 in formula (Ia) with the exception of a hydrogen atom,
- R_8 represents a hydrogen atom, a linear or branched, saturated or unsaturated, acyclic aliphatic group; a monocyclic or polycyclic, saturated or unsaturated carbocyclic group; a chain of the abovementioned groups.

10 - The method as claimed in claim 1, characterized in that the nucleophilic substrate corresponds to the formula below:

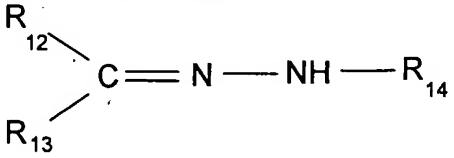


(Ie)

in said formula:

- R_9 , R_{10} and R_{11}, which may be identical or different, have the meaning given for R_1 and R_2 in formula (Ia).
- R_{11} represents a hydrogen atom or a protective group G,
- at most one of the groups R_9 and R_{10} represents a hydrogen atom,
- or else R_9 and R_{10} may be linked so as to constitute, with the carbon atoms that bear them, a monocyclic or polycyclic, saturated, unsaturated or aromatic, carbocyclic or heterocyclic group having from 3 to 20 atoms.

11 - The method as claimed in claim 1, characterized in that the nucleophilic substrate corresponds to the formula below:



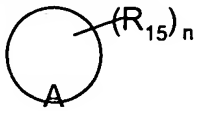
(If)

in said formula:

- R_{12}, R_{13} and R_{14}, which may be identical or different, have the meaning given for R_1 and R_2 in formula (Ia),
- at most one of the groups R_{12} and R_{13} represents a hydrogen atom,

- or else R_{12} and R_{13} may be linked so as to constitute, with the carbon atoms that bear them, a monocyclic or polycyclic, saturated, unsaturated or aromatic, carbocyclic or heterocyclic group having from 3 to 20 atoms.

12 - The method as claimed in claim 1, characterized in that the nucleophilic substrate corresponds to the formula below:



(Ig)

in said formula (Ig):

- A symbolizes the residue of a ring forming all or part of a monocyclic or polycyclic, aromatic or nonaromatic heterocyclic system in which one of the carbon atoms is replaced with at least one -NH group,
- R_{15}, which may be identical or different, represent substituents on the ring,
- n represents the number of substituents on the ring.

13 - The method as claimed in claim 12, characterized in that the nucleophilic substrate corresponds to formula (Ig) in which A represents a ring such as: imidazole, pyrazole, triazole, pyrazine, oxadiazole, oxazole, tetrazole, indole, pyrrole, phthalazine, pyridazine or oxazolidine.

14 - The method as claimed in claim 1, characterized in that the nucleophilic substrate is aniline, N-methylaniline, diphenylamine, benzylamine, dibenzylamine, N-methyl-N-phenylamine, benzophenone imine, benzophenone hydrazone, benzophenone oxime.

15 - The method as claimed in one of claims 1 to 14, characterized in that the unsaturated compound comprising a leaving group Y corresponds to formula (II):

$$R_0 - Y \quad (II)$$

in said formula (II):

- R_0 represents a hydrocarbon group comprising from 2 to 20 carbon atoms and has a double bond or a triple bond located in the α-position with respect to a leaving group Y or a monocyclic or polycyclic, aromatic carbocyclic and/or heterocyclic group bearing a leaving group on one ring.

16 - The method as claimed in claim 15, characterized in that the unsaturated

compound comprising a leaving group corresponds to formula (II) in which:

- R_0 represents an aliphatic hydrocarbon group comprising a double bond or a triple bond in the α-position with respect to the leaving group or an unsaturated cyclic hydrocarbon group in which an unsaturation bears the leaving group,
- R_0 represents a monocyclic or polycyclic, aromatic carbocyclic and/or heterocyclic group,
- Y represents a leaving group, preferably a halogen atom or a sulfonic ester group of formula $-OSO_2-R_e$, in which R_e is a hydrocarbon group.

17 - The method as claimed in either of claims 15 and 16, characterized in that the unsaturated compound comprising a leaving group corresponds to formula (II) in which Y represents a bromine or chlorine atom or a sulfonic ester of formula $-OSO_2-R_e$, in which R_e is a linear or branched alkyl group having from 1 to 4 carbon atoms, preferably a methyl or ethyl group, a phenyl or tolyl group or a trifluoromethyl group.

18 - The method as claimed in one of claims 15 to 17, characterized in that the unsaturated compound comprising a leaving group corresponding to formula (II) is chosen from the following compounds:

- (1) those of aliphatic type bearing a double bond that can be represented by formula (IIa):

$$R_{20} - C = C - Y \quad \text{(IIa)}$$
$$\phantom{R_{20} -} | \quad | $$
$$\phantom{R_{20} -} R_{21} \quad R_{22}$$

in said formula (IIa):

- R_{20}, R_{21} and R_{22}, which may be identical or different, represent a hydrogen atom or a hydrocarbon group having from 1 to 20 carbon atoms, which may be a linear or branched, saturated or unsaturated aliphatic group; a monocyclic or polycyclic, saturated, unsaturated or aromatic, carbocyclic or heterocyclic group; or a chain of aliphatic and/or carbocyclic and/or heterocyclic groups as mentioned above,
- Y symbolizes the leaving group as defined above,

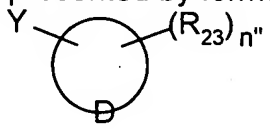
- (2) those of aliphatic type bearing a triple bond and that can be represented by formula (IIb):

$$R_{20} - C \equiv C - Y \quad \text{(IIb)}$$

in said formula (IIb):

- R_{20} has the meaning given in formula (IIa),
- Y represents a leaving group as defined above,

- (3) those of aromatic type that are subsequently referred to as "haloaromatic compound" and that can be represented by formula (IIc):



(IIc)

in which:

- D symbolizes the residue of a ring forming all or part of a monocyclic or polycyclic, aromatic carbocyclic and/or heterocyclic system,
- R_{23}, which may be identical or different, represent substituents on the ring,
- Y represents a leaving group as defined above,
- n" represents the number of substituents on the ring.

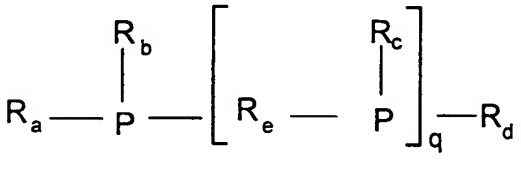
19 - The method as claimed in one of claims 15 to 18, characterized in that the leaving group-bearing compound corresponding to formula (II) is chosen from: vinyl chloride, vinyl bromide, bromoalkyne, iodoalkyne, β-bromostyrene, β-chlorostyrene, p-chlorotoluene, p-bromoanisole or p-bromotrifluorobenzene.

20 - The method as claimed in one of claims 1 to 34, characterized in that the catalyst comprises the metal element Pd introduced in the form of a finely divided metal or in the form of an inorganic derivative such as an oxide or a hydroxide; in the form of a mineral salt, preferably nitrate, sulfate, oxysulfate, halide, oxyhalide or carbonate; in the form of an organic derivative, preferably cyanide, oxalate, acetylacetonate; alkoxide, and even more preferentially methoxide or ethoxide; carboxylate, and even more preferentially acetate, or in the form of a complex, in particular a chlorinated or cyanated complex of Pd metals and/or of alkali metals, preferably sodium or potassium, or of ammonium.

21 - The method as claimed in claim 20, characterized in that the Pd element is introduced through palladium chloride, palladium acetate or palladium-on-charcoal.

22 - The method as claimed in one of claims 1 to 21, characterized in that the ligand is a phosphine or a phosphite or a phosphonite.

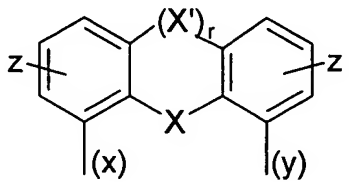
23 - The method as claimed in claim 22, characterized in that the phosphine corresponds to the formula below:



(IIIa)

in said formula:

- q is equal to 0 or 1,
- the groups R_a, R_b, R_c and R_d, which may be identical or different, represent:
  - . an alkyl group having from 1 to 12 carbon atoms,
  - . a cycloalkyl group having 5 or 6 carbon atoms,
  - . a cycloalkyl group having 5 or 6 carbon atoms, which is substituted with one or more alkyl groups having 1 to 4 carbon atoms, or alkoxy groups having 1 or 4 carbon atoms,
  - . a phenylalkyl group in which the aliphatic portion contains from 1 to 6 carbon atoms,
  - . a phenyl or biphenyl group,
  - . a phenyl or biphenyl group substituted with one or more alkyl groups having from 1 to 4 carbon atoms or alkoxy groups having from 1 to 4 carbon atoms, one or more halogen atoms, or a trifluoromethyl group,
- the group R_e represents:
  - . a valency bond or a saturated or unsaturated, linear or branched divalent hydrocarbon group having from 1 to 6 carbon atoms,
  - . an aromatic group of formula:



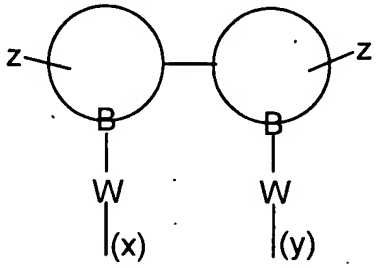
(IV)

in which:

- Z represents a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, a halogen atom or a trifluoromethyl group,

- X is an oxygen or sulfur atom or a linear or branched alkylene group having from 1 to 3 carbon atoms,
- if r is equal to 1, X' represents a valency bond, an oxygen, sulfur or silicon atom or a linear or branched alkylene group having from 1 to 3 carbon atoms,
- if r is equal to 0, the two rings are not linked,
- (x) and (y) pinpoint respectively the two bonds established between the group R_e symbolized by formula (IV) and the phosphorus atoms,

. an aromatic group of formula:

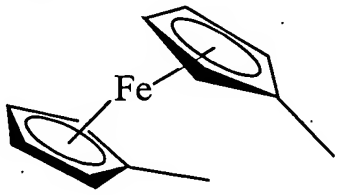


(V)

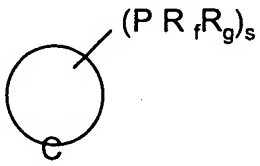
in which:

- Z has the meaning given above,
- B represents the residue of a benzene or naphthalene ring,
- W represents a valency bond or a linear or branched alkylene group having from 1 to 3 carbon atoms,
- (x) and (y) pinpoint respectively the two bonds established between the group R_e symbolized by formula (V) and the phosphorus atoms,

. a ferrocene group of formula:



24 - A method as claimed in claim 22, characterized in that the phosphine corresponds to the formula below:

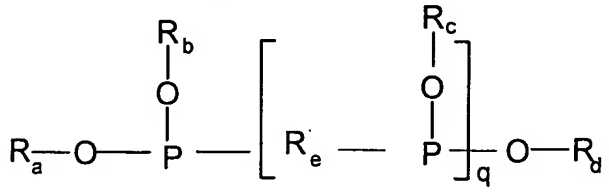


(IIIb)

in which:

- C represents the residue of a pentane or cyclohexane ring,
- R_f and R_g, which may be identical or different, have the meaning given for R_a or R_b, in formula (IIIa),
- s is a number equal to 1 to 6, preferably equal to 4.

25 - The method as claimed in claim 22, characterized in that the phosphonite corresponds to the formula below:



(IIIc)

in said formula, the groups R_a, R_b, R_c, R_d and R_e, and the symbol q have the meaning given for formula (IIIa).

26 - The method as claimed in one of claims 22 to 25, characterized in that the ligand is chosen from: tricyclohexylphosphine, trimethylphosphine, triethylphosphine, tri-*n*-butylphosphine, triisobutylphosphine, tri-*tert*-butylphosphine, tribenzylphosphine, dicyclohexylphenylphosphine, 2-dicyclohexylphosphino-2-methylbiphenyl, triphenylphosphine, dimethylphenylphosphine, diethylphenylphosphine, di-*tert*-butylphenylphosphine, tri(p-tolyl)phosphine, isopropyldiphenylphosphine, tris(pentafluorophenyl)phosphine, tri(o-tolyl)phosphine, bisdiphenylphosphinomethane, bisdiphenylphosphinoethane, bisdiphenylphosphinopropane, bisdiphenylphosphinobutane, bisdiphenylphosphinopentane, bisdiphenylphosphinoferrocene, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), bis-[(2-diphenylphosphino)phenyl] ether (DPEPHOS), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XANTPHOS), tetrakis-(2,4-di-tert-butylphenyl)-4,4'-diphenylenebisphosphonite.

27 - The method as claimed in one of claims 1 to 26, characterized in that the base is an ammonium hydroxide or a hydroxide of a monovalent metal and/or of a bivalent metal, preferably an alkali and/or alkaline earth metal.

28 - The method as claimed in claim 27, characterized in that the base is sodium hydroxide.

29 - The method as claimed in either of claims 27 and 28, characterized in that the base is introduced in a solid form or in a solution.

30 - The method as claimed in one of claims 1 to 29, characterized in that the solvent is a mono- or a polyalcohol, an ether alcohol or an amino alcohol, or mixtures thereof.

31 - The method as claimed in claim 30, characterized in that the alcohol corresponds to the formula below:

$$R_h - OH \quad (VI)$$

in said formula (VI):

- R_h represents an optionally substituted hydrocarbon group having from 1 to 24 carbon atoms, which may be a linear or branched, saturated or unsaturated acyclic aliphatic group; a monocyclic or polycyclic, saturated or unsaturated cycloaliphatic group; or a linear or branched, saturated or unsaturated aliphatic group bearing a cyclic substituent.

32 - The method as claimed in claim 31, characterized in that the alcohol is a primary alcohol or secondary alcohol that is hindered or a tertiary alcohol.

33 - The method as claimed in claim 30, characterized in that the solvent is n-butanol, tert-butanol, ethylene glycol, N,N-dimethylethanolamine; methoxyethanol, 1-methoxypropan-2-ol, but preferably tert-butanol or tert-amyl alcohol.

34 - The method as claimed in either of claims 27 and 28, characterized in that the base is introduced in the form of a suspension in the alcohol as defined in one of claims 30 to 33.

35 - The method as claimed in one of claims 27 to 34, characterized in that reactive milling of the metal hydroxide or ammonium hydroxide and of the alcohol is carried out.

36 - The method as claimed in one of claims 27 to 35, characterized in that reactive milling of sodium hydroxide (already milled or in the form of pellets) and of tert-amyl alcohol or tert-butanol is carried out.

37 - The method as claimed in claim 1, characterized in that the amount of compound introducing the Pd element, that is used, expressed by the molar ratio of the number of moles of said Pd compound to the number of moles of compound of formula (II), ranges between 0.005 and 1, preferably between 0.01 and 0.1.

38 - The method as claimed in either of claims 35 and 36, characterized in that the amount of compound introducing the Pd element, that is used, expressed by the molar ratio of the number of moles of said Pd compound to the number of moles of compound of formula (II), ranges between 0.005 and 0.5, preferably between 0.005 and 0.01.

39 - The method as claimed in claim 1, characterized in that the alcohol-type solvent is combined with an apolar aprotic solvent.

40 - The method as claimed in claim 39, characterized in that the apolar aprotic solvent is an aliphatic, cycloaliphatic or aromatic hydrocarbon.

41 - The method as claimed in either of claims 39 and 40, characterized in that the polar aprotic solvent is an aliphatic hydrocarbon, preferably hexane, cyclohexane, methylcyclohexane, or petroleum cuts of the petroleum ether type; an aromatic hydrocarbon, preferably benzene, toluene, xylenes, cumene, mesitylene, or petroleum cuts consisting of a mixture of alkylbenzenes, in particular cuts of Solvesso type.

42 - The method as claimed in one of claims 1 to 40, characterized in that the amount of cosolvent used represents from 1 to 50% of the volume of the alcohol-type solvent, preferably from 10 to 20%.

43 - The method as claimed in one of claims 1 to 42, characterized in that the coupling reaction between the nucleophilic compound and the leaving group-bearing unsaturated compound takes place at a temperature which is chosen such that the reactants are maintained in the liquid state.

44 - The method as claimed in claim 43, characterized in that the coupling reaction

between the nucleophilic compound and the leaving group-bearing unsaturated compound takes place at a temperature which is advantageously situated between 50°C and 200°C, preferably between 80°C and 150°C, and even more preferentially between 90°C and 110°C.

45 - The method as claimed in one of claims 1 to 44, characterized in that the leaving group-bearing unsaturated compound, preferably of formula (II), the base, the alcohol-type solvent and, optionally, the cosolvent are loaded; the compound introducing the Pd metal element and the ligand or else the preformed metal complex are added separately to the medium; the reaction medium is brought to the selected reaction temperature; the nucleophilic compound, preferably of formula (Ia) to (Ig), is subsequently added and the coupling product obtained is then recovered.

46 - The method as claimed in one of claims 1 to 45, characterized in that the coupling product obtained is benzophenone N-p-tolylhydrazone, benzophenone N-phenylhydrazone, benzophenone N-p-methoxyphenylhydrazone, benzophenone N-o-tolylhydrazone, benzophenone N-p-fluorophenylhydrazone, benzophenone N-4-fluoro-3-chlorophenylhydrazone, benzophenone N-2-fluoro-5-chlorophenylhydrazone, or benzophenone N-4-fluoro-3-cyanophenylhydrazone.